## REQUEST FOR RECONSIDERATION

Claims 3 to 8 as presented with applicants' Request for Continued Examination dated September 19, 2005, are currently pending in this application. Claims 1 and 2 were canceled at that time.

The Examiner reiterated the position that the subject matter of applicants' Claims 3 to 8 was unpatentable under 35 U.S.C. §103(a) in light of the teaching of ***Novack*** **(US 3,649,628)**.

When applying 35 U.S.C. §103, it is inter alia necessary that references be considered as a whole, that the references suggest the desirability and thus the obviousness of making the claimed combination, and that the references be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.[1] Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.[2] The mere fact that the prior art could be so modified would not make the modification obvious unless the prior art suggests the desirability of the modification.[3] It is insufficient that the prior art discloses the components of the claimed invention, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor.[4] Also, certain basic criteria have to be met to establish a *prima facie* case of obviousness.[5]

When the teaching of ***Novack*** is evaluated from the standpoint of a person of ordinary skill at the time applicants made their invention, ie. a person who is not imbued with knowledge available only from applicants' disclosure of their invention, it is immediately apparent that the reference fails to establish a prima facie case of obviousness because it fails to teach or suggest all of the elements which are recited in applicants' claims, and it also fails to provide the suggestion or motivation which is necessary for a person of ordinary

1) *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

2) *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 466 (Fed. Cir. 1986).

3) *In re Laskowski*, 871 F.2d 115, 10 USPQ2d 1397 (Fed. Cir. 1989).

4) *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 15 USPQ2d 1321 (Fed. Cir. 1990), *cert. denied* 498 U.S. 920 (1990).

5) Cf. applicants' paper of October 23, 2006, page 4. The paper is herewith incorporated by reference.

skill in the art to do what applicants have done. The reference fails, in particular, to teach or suggest a procedure in which

1) a carboxylic acid in amounts of from 0.75 to 2.0 equivalents per mole of ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate is added to a solution of a contaminated cis/trans mixture of the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water immiscible solvent, and/or

2) a mixture obtained in accordance with (1) is stirred for 0.5 to 2 hours at a temperature of from 50°C to 100°C,

to selectively convert the ethyl 3-dimethylamino-2-phenyl-propionate into ethyl atropate by eliminating dimethyl amine without essentially affecting the cis/trans ratio of the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate.[6]

***Novack*** teaches a process for the preparation of, inter alia, 3-dimethylamino-4-phenyl-4-carbethoxy-$\Delta^1$-cyclohexene and provides information pertaining to:

a) the reactions involved in the synthesis of the respective product,[7]

b) the separation and isolation of the product (in form of a mixture of the cis- and trans-isomers) from the reaction mixture obtained in (a),[8]

c) the separation of the trans-isomer from the cis/trans mixture obtained in (b),[9] and

d) the purification of the trans-isomer.[10]

Additionally, ***Novack*** inter alia mentions that the base form of the product can be converted into pharmaceutically acceptable acid addition salts which are suitable for incorporation into dosage forms.[11]

The Examiner took the position that the information given by ***Novack*** as concerns the pharmaceutically acceptable acid addition salts

6) Cf. current Claim 3 which is the sole independent claim currently pending in the application.

7) E.g. col. 2, indicated line 33, to col. 3, indicated line 62, and col. 6, indicated lines indicated lines 23 to 37, of ***US 3,649,628***.

8) E.g. col. 3, indicated line 63, to col. 4, indicated line 19, and col. 6, indicated lines 38 to 60, of ***US 3,649,628***.

9) E.g. col. 4, indicated line 20, to col. 5, indicated line 10, and col. 6, indicated line 65, to col. 7, indicated line 27, of ***US 3,649,628***.

10) E.g. col. 5, indicated lines 29 to 56, and col. 7, indicated lines 29 to 67, of ***US 3,649,628***.

11) E.g. col. 5, indicated lines 11 to 28, of ***US 3,649,628***.

which is found in col. 5, indicated lines 24 to 28, of the reference:

*Such acids include, for example, inorganic acids, such as, hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, etc. and organic acids, such as, acetic acid, benzoic acid, citric acid, maleic acid, salicylic acid, tartaric acid, etc.*

supported that hydrochloric acid and carboxylic acids were equivalents, and argued that a person of ordinary skill in the art would therefore have replaced the hydrochloric acid which is employed in the separation step (b) of ***Novack***'s process by a carboxylic acid.

As noted in the foregoing, it is not sufficient for a finding of obviousness under Section 103(a) that the prior art discloses the components of the claimed invention, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor. Clearly, **Novack** discloses the respective components of applicants' invention in a different combination, and there is no teaching, suggestion, or incentive to make the combination made by applicants. The pertinent steps of the separation (b) of ***Novack***'s process are described as follows:[12)]

*Extract the benzene layer [containing the cis- and trans-isomers of the product] with 2 portions of 1 N hydrochloric acid (22 liters and 3 liters respectively). The benzene layer is discarded. The acid extracts are combined and washed with 4.5 liters of benzene. Separate the benzene layer and discard.*

*Basify the aqueous with 1.4 liter of 50% aqueous sodium hydroxide. Extract the aqueous with 2 portions of petroleum ether (11.5 liters and 6 liters respectively). Discard the aqueous layer.*

It is immediately apparent to a person of ordinary skill in the chemical art that the hydrochloric acid serves in the separation (b) to convert the product into a form which is soluble in the aqueous phase but insoluble in the benzene layer. The utilization of an organic acid instead of hydrochloric acid in the formation of the salt and the initial extraction, on the one hand, increases the lipophilic character of the salt, and on the other hand, increase the likelihood that the acid is taken up by the benzene phase.[13)] In either case, the the separation of the product salt from the benzene phase is likely to be less complete than the separation which is achieved with hydrochloric acid. Moreover, the product salt which is formed in the ini-

12) Cf. col. 6, indicated lines 41 to 48, of ***US 3,649,628***.

13) Benzene is miscible with glacial acetic acid.

tial extraction of the separation (b) is subsequently treated with a base to liberate the product. The suitability of organic acids for purposes of pharmaceutically acceptable forms of the product can, therefore, also not render the modification of the acid employed in ***Novack***'s step (b) desirable or obvious.

The Examiner's position that *"the skilled artisan in the art would expect such a modification to be feasible and successful"*[14] is, in light of the foregoing, clearly in error. Moreover, as noted in the foregoing, the mere fact that the prior art could be so modified would not make the modification obvious unless the prior art suggests the desirability of the modification. No such suggestion is found in the reference.

Furthermore, the Examiner took the position that the information which is given by ***Novack*** concerning the synthesis stage (a) in col. 6, lines 36 and 37, of the reference would have motivated a person of ordinary skill in the art to stir a mixture of organic acid, contaminated cis/trans mixture of the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate, and water immiscible solvent for 0.5 to 2 hours at a temperature of from 50°C to 100°C as is required in accordance with applicants' process. Again, the Examiner combined components of the prior art which are disclosed in the reference in other combinations in an attempt to recreate the elements of applicants' invention. As noted, the section of ***Novack***'s teaching upon which the Examiner relied in this context pertains to the reaction of ethyl atropate[15] with a product obtained by reacting crotonaldehyde[16] and dimethylamine:[17],[18]

> *Upon completion [of the reaction of crotonaldehyde and dimethylamine], stir for 15 minutes and flush the system thoroughly with nitrogen. Add, all at once 3660 grams (18.95 mols) of ethyl atropate (91.2% purity by GLC) and heat to about 75°C (15 minutes). Remove external heating and allow the reaction temperature to rise to 90°C and control by external cooling. <u>When the reaction is no longer exothermic, maintain at 90°C to 95°C for 2 hours</u>.*

14) Office action page 4, lines 8 to 10.

15) Representative of the compounds generically represented by ***Novack***'s formula (IV); cf. col. 2, indicated lines 45 to 52, of ***US 3,649,628***.

16) Representative of the compounds generically represented by ***Novack***'s formula (III); cf. col. 2, indicated lines 41 to 44, of ***US 3,649,628***.

17) Representative of the compounds generically represented by ***Novack***'s formula (II); cf. col. 2, indicated lines 35 to 40, of ***US 3,649,628***.

18) Col. 6, indicated lines 30 to 37, of ***US 3,649,628***; emphasis added.

The Examiner asserted *"the specification of the prior art does teach that the reaction temperature is allowed to raise to 90 to 95°C for 2 hours (...), which is very similar to the reaction conditions in the claimed invention."*[19] However, any similarity starts and ends with the temperature and the time. The reaction mixture which is, in accordance with the teaching of ***Novack***, exposed to the said temperature for the specified time does not comprise any organic or inorganic acid. In fact, the reaction of crotonaldehyde and dimethylamine is conducted in the presence of potassium carbonate,[20] and the respective mixture is, therefore, clearly not acidic. Moreover, the reference contains nothing which could reasonably be considered as a suggestion or motivation to apply the respective temperature for the referenced period of time to the acid extraction which is conducted in the separation (b), ie. the steps:[21]

> *Extract the benzene layer [containing the cis- and trans-isomers of the product] with 2 portions of 1 N hydrochloric acid (22 liters and 3 liters respectively). The benzene layer is discarded. The acid extracts are combined and washed with 4.5 liters of benzene. Separate the benzene layer and discard.*
> *Basify the aqueous with 1.4 liter of 50% aqueous sodium hydroxide. Extract the aqueous with 2 portions of petroleum ether (11.5 liters and 6 liters respectively). Discard the aqueous layer.*

An increase of the temperature of the benzene / hydrochloric acid system of the initial extraction increases the solubility and, thereby, jeopardizes the success of the extraction.

Again, it is not sufficient for a finding of obviousness under Section 103(a) that the prior art discloses the components of the claimed invention, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor. The information regarding the temperature and time on the one hand, and regarding the addition of hydrochloric acid on the other hand, is disclosed by **Novack** in completely different contexts, and the reference contains no teaching, suggestion, or incentive whatsoever which would have motivated a person of ordinary skill to apply the respective temperature for the specified time to the extraction mixture in the separation (b) of ***Novack***.

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19) Office action page 4, lines 12 to 14.

20) Cf. col. 6, indicated line 27, of ***US 3,649,628***.

21) Cf. col. 6, indicated lines 41 to 48, of ***US 3,649,628***.

To establish a *prima facie* case of obviousness, all of the following criteria have to be met:

(1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings,

(2) there must be a reasonable expectation of success, and

(3) the prior art reference or the combined references must teach or suggest all of the claim limitations.

Additionally, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and cannot be based on the applicant's disclosure.[22)]

The foregoing analysis shows that neither the reference nor the knowledge generally available to one of ordinary skill in the art can reasonably be deemed to provide the necessary suggestion or motivation to do what applicants have done. In fact, each of the purportedly obvious modifications of ***Novack***'s process jeopardize the success of the separation step (b) which is modified in accordance with the Examiner's argument. The reference would therefore appear to teach away from the claimed invention rather than rendering it obvious as the Examiner would have it. Correspondingly, the reference clearly fails to teach or suggest all of the limitations which are set forth in applicants' claims, in particular

1) adding certain amounts of a carboxylic acid to a solution of a contaminated cis/trans mixture of the ethyl 2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate in a water immiscible solvent, and/or

2) stirring a mixture obtained in accordance with (1) for 0.5 to 2 hours at a temperature of from 50°C to 100°C.

The teaching of ***Novack*** is, accordingly, unsuited to establish that the subject matter of applicants' Claims 3 to 8 was prima facie obvious at the time the invention was made.

It is therefore respectfully requested that the rejection of Claims 3 to 8 under Section 103(a) be withdrawn. Favorable action is solicited.

22) *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).